REMARKS/ARGUMENTS

Status of the Claims

Claims 17, 32, 33 and 40-46 were previously pending and presented for examination. Claims 17 and 44 are amended. Claims 32, 33, 42, 43, 45, and 46 are canceled without prejudice. Claim 47 is newly presented. After entry of these amendments, claims 17, 40, 41, 44, and 47 will be pending and presented for examination.

The claims stand rejected under 35 U.S.C. §112, 2nd paragraph for alleged indefiniteness.

The claims stand rejected under 35 U.S.C. §112, 1st paragraph as allegedly not enabled.

Applicants respectfully respond to these rejections below.

Applicants further thank the Examiner for considering the previously submitted Affidavit and, without acquiescing to the position of the Examiner, further address such issues as they related to the instant grounds for rejection.

Support for the Claims

Support for the subject matter of amended claim 17 is found *inter alia* in the previous version of the claim and in the specification. The subject matter of *completely* attenuating or completely inactivating a virus is set forth in the specification at p. 8, line 28. The lower limit of 10 femtograms is set forth for both attenuated and inactivated virus is found in the paragraph bridging pages 14 and 15; the upper limit of 1 pg is derived from the lower range of the amount required to set off a humoral response (see page 14, line 8). In addition, support for the subject matter of "lacks a portion of a gene coding for a gag nucleocapsid protein" is found *inter alia* in previous claim 33.

Claim 44 is amended to conform to a change in the antecedent basis of amended claim 17.

Support for the subject matter of new claim 47 is found *inter alia* in previous claim 17 and in the specification in the paragraph bridging pages 16 and 17 and in the first full paragraph of page 18.

In view of the above, Applicants believe the amendments to the claims add no new matter and respectfully request their entry.

Response to the Rejection for Alleged Indefiniteness

The Action alleges that the recital "sufficient to induce a cell mediated response against said-virus but below the amount necessary to induce an offsetting humoral response to said-virus" was indefinite. In order to expedite prosecution of the instant application, and without acquiescing to the Action on this point, the Applicants have amended the base claim to remove the recital at issue.

Applicants note that new dependent claim 47 sets forth a similar recital. However, the subject matter thereof has been further delimited to address the concern raised by the Examiner.

In light of the above, Applicants request that the above rejection be reconsidered and withdrawn.

Response to the Rejection for an Alleged Lack of Enablement

As noted by both the Examiner and Applicant previously, whether undue experimentation is required to practice an invention is typically determined by evaluating: (i) the relative skill of those in the art; (ii) the nature of the invention; (iii) the breadth of the claims; (iv) the amount of guidance presented; (v) the presence of working examples; (vi) the state of the art; (vii) the predictability of the art; and (viii) the quantity of experimentation necessary. *Ex parte*

Forman, 230 U.S.P.Q. 546 (PTO Bd. Pat. App. & Inter. 1986), *In re Wands*, 858 F.2d 731, 8 U.S.P.Q.2d 1400 (Fed. Cir. 1988). Without belaboring earlier remarks, Applicants turn now to address each of the Examiner's present concerns as they touch upon these factors.

The first concern asserts that the Applicants failed to provide any guidance as to the correlates of human protection. This assertion is not correct. Throughout the specification, the claimed invention is predicated on the principle that cell-mediated immunity is a correlate of protection and that low doses of HIV immunogen can selectively induce a cell-mediated immune response as opposed to a humoral response. The specification relates SIV studies which serve as a model to support this proposition. Furthermore, the prosecution history relates the natural experiments which have occurred in HIV-exposed and infected individuals who are protected by a cell-mediated immune responses to HIV. Moreover, the Applicants are not required to teach how their invention works by demonstrating in any detail which components of the immune system are necessary and sufficient to provide protection from natural infection. Applicants need only disclose a method that works, not the details of how it works.

The second concern challenges the breadth of protection afforded by the method in view of the quasi-species nature of HIV. However, patentability is not predicated on how well or broadly a claimed invention works, only on whether the invention works to some extent (see MPEP §2107.01 II: Wholly Inoperative Inventions: Incredible Utility at 2100-33, May 2004 Edition). A vaccine need not be universally effective to be patentable. Even a limited utility suffices. For instance, a person vaccinated against one particular strain of HIV may have limited protection for some other variants of that strain of HIV and less or no protection against other, more different strains of HIV. However, the claim is directed toward vaccination against a HIV. A vaccinated individual derives a substantial benefit even protected against only the administered strain. Furthermore, Applicants note that dependent claims are drawn to HIV-1 and HIV-2.

The Action also does not conform with much public health practice. For instance, the flu vaccine is still useful even if it only lessons the severity of a disease, does not protect against all flu strains, and has a limited duration (from season to season).

The third concern posits the specification provides insufficient guidance as to factors governing the pathogenesis of HIV-induced disease. Many of the cited factors bear more on the *safety* of the vaccine, rather than its *efficacy*. As noted previously, safety is within the province of the Food and Drug Administration, not the Patent Office[1]. Nevertheless, to the extent that safety and/or efficacy and the choice of immunogen are at issue, the claims have been amended to set forth that a completely attenuated or inactivated virus is administered. In addition, the myriad factors cited by the Examiner would generally apply to the many other types of HIV vaccines currently undergoing clinical trials (*see*, for instance, the NIH's HIV Vaccine Development Status Report, May 2000, already of record). The existence of such trials evidences that the concerns of the Examiner are no bar to clinical studies and, hence, should be no bar to patentability as well[2].

The fourth concern posits that efficacy need be demonstrated in a Phase III clinical trial. This requirement is contrary to the law. The Courts have recognized that entry into Phase I and Phase II clinical trials is evidence of sufficient expectation of success as to establish enablement. In the therapeutic arts, the courts have held that for public policy reasons the necessary showing for enablement does not require testing in humans. The Federal Circuit has held:

> Usefulness in patent law, and in particular in the context of pharmaceutical inventions, necessarily includes the expectation of further research and development. The stage at which an

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[1] *See Scott v. Finney,* 34 F.3d 1058, 1063, 32 USPQ2d 1115, 1120 (Fed. Cir. 1994) ("Testing for the full safety and effectiveness of a prosthetic device is more properly left to the Food and Drug Administration (FDA). Title 35 does not demand that such human testing occur within the confines of Patent and Trademark Office (PTO) proceedings.").

[2] As provided in MPEP § 2107.3 Part IV:

Before a drug can enter human clinical trials, the sponsor, often the applicant, must provide a convincing rationale to those especially skilled in the art (e.g., the Food and Drug Administration) that the investigation may be successful. Such a rationale would provide a basis for the sponsor's expectation that the investigation may be successful. In order to determine a protocol for phase I testing, the first phase of clinical investigation, some credible rationale of how the drug might be effective or could be effective would be necessary. Thus, as a general rule, if an applicant has initiated human clinical trials for a therapeutic product or process, Office personnel should presume that the applicant has established that the subject matter of that trial is reasonably predictive of having the asserted therapeutic utility.

> invention in this field becomes useful is well before it is ready to be administered to humans. Were we to require Phase II testing in order to prove utility, the associated costs would prevent many companies from obtaining patent protection on promising new inventions, thereby eliminating an incentive to pursue, through research and development, potential cures in many crucial areas such as the treatment of cancer (In re Brana 34 U.S.P.Q. 2nd 1436 (Fed. Cir. 1995)).

The Action would make a distinction between enablement in animals and humans which is simply not consistent with legal precedent. In fact, the Brana Court brooked no such broad distinction between efficacy in animals and humans:

> Patent and Trademark Office improperly rejected, for lack of utility, application claims for pharmaceutical compounds used in cancer treatment in humans, since neither nature of invention nor evidence proffered by PTO would cause one of ordinary skill in art to reasonably doubt asserted utility, and since even if utility of compounds could be reasonably questioned, evidence that compounds within scope of claims, and other structurally similar compounds, are effective as chemotherapeutic agents in animals would be sufficient to convince one skilled in art of asserted utility; absence of evidence that claimed compounds have chemotherapeutic effect in humans does not warrant contrary conclusion, since proof of alleged pharmaceutical property for compound by statistically significant tests using standard experimental animals is sufficient to establish utility.

(see first paragraph of the decision in *Brana*).

The above is also essentially in accord with the guidance of MPEP § 2107.3 Part IV.

With respect to the above holding, the Feinberg and Moore (2000) reference is more fairly construed as supporting the patentability of the instantly claimed subject matter. Indeed, Feinberg and Moore state: *"Animal models are an essential resource for evaluating the safety and comparative immunogenicity of candidate AIDS vaccine strategies in preparation of Phase I human studies."* (see Feinberg at p. 209, first sentence last full paragraph of column 1.).

The fifth concern posits that the Applicants provide insufficient guidance as to the ability of any given immunogen to induce a cell-mediated immune response as opposed to a humoral response, Applicants respectfully point out that the claims are now drawn to completely attenuated or inactivated virus. These attenuated and inactivated viruses comprise nearly all the components of HIV, save for those necessary to cause disease and present relatively few

selection issues of the kind identified by the Examiner. For instance, as taught in the specification, inactivation of HIV renders it harmless as an infectious biological agent but does not destroy its immunogenicity (see paragraph bridging pages 9 and 10). Such immunogens differ very slightly from the immunogens of the corresponding live viruses which have been observed to selectively produce a cell-mediated immunity at low doses in model systems and in human epidemiological investigations.

The sixth concern posits that the Applicants do not provide sufficient guidance as to the nature of the immunogen. Applicants note that the claims are drawn to administration of completely attenuated or inactivated virus which, again, comprise nearly all the components of HIV, save for those necessary to cause disease. Very little selection is involved.

As a seventh concern, the Action would extend the alleged failure of a number of clinical studies in the HIV field to the claimed subject matter. This approach is exactly wrong. In view of the above-cited legal precedent, the existence of such studies in and of themselves is strong as evidence as to enablement of their particular subject matter, especially as of the time of filing, regardless of the later outcome of such studies.

Applicants further note that the criteria for a successful Phase III clinical trial is not merely demonstrating that the vaccine works at all (the criterion for patentability), but includes whether a vaccine provides a sufficient degree of efficacy in a sufficient proportion of the test population to outweigh any health risks. The standard for patentability is simply not the same as that for a successful Phase III clinical trial. To require evidence of a successful Phase III clinical trial is, as noted above, contrary to the public policy behind the law and can serve only to impede the development of much needed vaccines.

As for the eight concern, without acquiescing to the position of the Examiner with respect to the breadth of the attenuated immunogen subject matter, the Applicants have amended the base claim without prejudice. As amended, the claim recites "a completely attenuated form of the virus ...wherein the attenuated form of the virus lacks a portion of a gene coding for a *gag* nucleocapsid protein."

Turning now to the last concern which addresses the absence of working embodiments, Applicants acknowledge that the specification does not provide a working embodiment of the claimed methods in humans[3]. However, the specification does describe the operability of the method in the SIV macaque model. More importantly, the subsequent epidemiological and clinical studies as set forth in the previously provided Affidavit provide substantial evidence that the claimed method would work in the human for HIV. Moreover, the specification does provides several prophetic Examples.

Generally, almost all the points raised by the last Action relate, to the state of the art in the relevant field. Whatever the Examiner's assessment of the art, it has been sufficiently mature to support the initiation of a many Phase I, II, and/or III clinical studies. In consideration of the existing legal precedent, the general state of the art can not be fairly viewed to bar patentability under 35 U.S.C. §112, first paragraph.of the instant claims.

In view of the above remarks and amendments, the Applicants respectfully request that the above grounds for rejection be reconsidered and withdrawn.

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[3] A long line of cases conclusively holds that working examples are not required to enable a claimed invention if the invention is otherwise disclosed. *See, e.g., In re Strahilevitz*, 212 U.S.P.Q. 561,563 (C.C.P.A. 1982) ("We recognize that working examples are *desirable* in complex technologies and that detailed examples can satisfy the statutory enablement requirement. ... Nevertheless, as acknowledged by the board, examples are not *required* to satisfy § 112, first paragraph.") (italics emphasis in original); *In re Borkowski*, 164 U.S.P.Q. 642, 645 (C.C.P.A. 1970) ("a specification need not contain a working example if the invention is otherwise disclosed"); *In re Long*, 151 U.S.P.Q. 640, 641 (C.C.P.A. 1966). *See* MPEP §2164.02.

CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 925-472-5000.

Respectfully submitted,

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